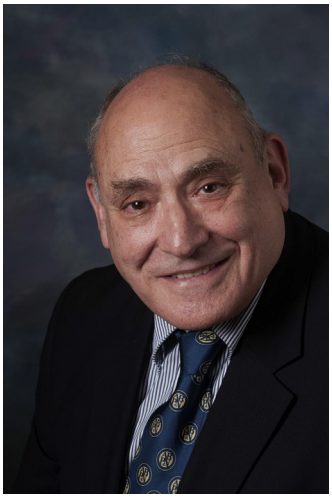
Editor-in-Chief's Note

Further Thoughts about Opioids and Cannabinoids

OH CANNABIS
Oh cannabis, oh cannabis
How countless are your products
Your many forms, so hard to choose
Your many claims, which to believe?
Potential harms, much yet unknown
Oh cannabis, oh cannabis
Should we be safe, or sorry?

Can be sung to the melody of "Oh Tannenbaum."
Based on a 16th century German folk song.



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One of the delicious meals my wife prepares features a dish called Jerusalem chicken. Its distinctive characteristic is its "licoricey" taste and aroma imparted by slices of fennel bulbs and liberal splashes of the liqueur Pernod. Recently, I purchased for her a small bottle of anise oil to further enhance this dish's flavor. When I arrived home, I decided to look into the differences among these licorice-like products. Fennel is a bulb-like vegetable that resembles aspects of onion, celery, and dill. Although it provides an anise aroma, it does not impart much of the taste of licorice. Pernod is made from star anise oil plus other ingredients. It is the successor to absinthe, a popular drink from the late 18th century. It was so popular that many paintings were made of absinthe drinkers in the 19th and early 20th centuries, the most well-known being *L'Absinthe* by Edgar Degas.[1] Other familiar star anise–flavored drinks include anisette, arak, Sambuca, pastis, and ouzo. Star anise is also a key ingredient in Chinese five-spice mix. Anise, the source of anise oil, is a parsley family herb. Fennel, anise, and star anise have in common anethole, an aromatic, unsaturated ether.[2,3] Anethole is poorly soluble in water; hence, the milky coloring that occurs when water is added to any of these drinks.

Licorice is an extract of *Glycyrrhiza glabra* roots. Along with other ingredients, including anise oil, it is sometimes used as a confectionary. Licorice extract itself also contains anethole. In 2012, the US Food and Drug Administration (FDA) issued a warning entitled, *Black Licorice: Trick or Treat?*[4] The sweetness of licorice results from glycyrrhizin, a compound that can dangerously lower potassium levels, causing cardiovascular complications such as hypertension, arrhythmias, and congestive heart failure.[5] The warning does not apply to red licorice candy, which is unlike black licorice except in its texture and flavor; it does not contain anethole or glycyrrhizin. Its sweetness comes from corn syrup and sugar.[6]

OPIOIDS

What has all of this to do with the primary focus of this Note on opioids and cannabis? When I opened the bottle of anise oil to taste it, it triggered a strong childhood memory of paregoric. Paregoric contains anise oil plus tincture of opium; it also contains camphor.[7] As a young child, I remember being given paregoric frequently for toothaches or

bouts of diarrhea. Years later, we also rubbed it on the gums of our own children when they were teething; it was still available without a prescription (until 1970).

During my early adolescent years, another opioid was frequently given to me for coughs, wild cherry—flavored hydrocodone combined with homatropine (Hycodan®); it was first approved and marketed in 1943.[8] At that time, the FDA did not require that drug approvals needed to be based on evidence of both safety and efficacy. I do not recall that my parents ever said they were worried that I might become addicted. Hycodan tablets were voluntarily removed by their manufacturer, Endo Pharmaceuticals (Malvern, Pennsylvania), in 2007–2008. I have been unable to locate any explanation for their decision. In January 2008, the FDA placed both the tablets and the oral formulation sold by Endo Pharmaceuticals on their Discontinued Product List, and all makers of unapproved hydrocodone-containing products were ordered to stop manufacturing them by December 31, 2007.[9] The FDA's action applied to all hydrocodone-containing products that as of that time had not demonstrated both safety and efficacy. In 2011, however, the FDA made it clear that their 2008 action was not taken for reasons of safety or effectiveness.[10,11] Other tablet and liquid forms of hydrocodone from other manufacturers that had undergone FDA vetting remained available. One example is Lortab® Elixir (hydrocodone bitartrate and acetaminophen oral solution; Akorn Pharmaceuticals, Lake Forest, Illinois), a yellow-colored, tropical fruit punch—flavored liquid that is indicated for pain relief.[12] Endo Pharmaceuticals reintroduced their hydrocodone with homatropine products in August 2008 for children ages 6 years and older and adults with cough as its sole indication.[13] This seems to have been the result of an ANDA (Abbreviated New Drug Application) filing.[14] Curiously, a hydrocodone without homatropine product, also called Hycodan, is marketed for cough in Canada by Bristol-Myers Canada (Laurent, Quebec, Canada).[15]

According to the 2019 MEPS (Medical Expenditure Panel Survey)[16] prescribed medicines file released annually by the US Government, the combination of hydrocodone and acetaminophen is 13th among the 300 most frequently prescribed medicines (>43 million prescriptions) in the United States. This combination is used to treat pain. The combination of oxycodone with acetaminophen (eg, Percocet® [Endo Pharmaceuticals]) does not appear in the top 300 list. However, oxycodone without acetaminophen is ranked at 52 (>14.6 million prescriptions). Hydrocodone consumption has regularly exceeded oxycodone consumption over the last 20 years, although this difference has almost annually narrowed during those years.[17,18] Qualitative data suggest that the overall amount of opioid availability is such that people usually do not have to go beyond their social networks (ie, friends, relatives) to find others who will sell or share these drugs.[17] Pain relief is commonly cited as the initial reason for misuse.

In a study of almost 15,000 adolescents and young adults who were prescribed an opioid (usually hydrocodone with acetaminophen or oxycodone with acetaminophen) by dental clinicians in conjunction with third molar extractions, there was a high rate of subsequent use, abuse, or misuse.[19] A notable risk factor was being female. In a smaller, yet somewhat comparable, study of adolescent and young adults undergoing general surgical procedures, persistent use of opioids was also observed, particularly after cholecystectomies and colectomies; again, being female was a risk factor.[20] Both studies emphasize the need for postprocedure monitoring when opioids have been prescribed. The Academy of General Dentistry has added a caveat to the study findings by Schroeder et al[19]: they point out that dental procedures typically result in a single prescription.[21] The Academy of General Dentistry suggests that single-event prescribing should be less problematic than when opioids are prescribed for chronic conditions requiring refills.

It is understandable that in some instances, opioids may be the only medications strong enough to relieve pain. However, it may not be necessary for them to be used as often as they are for athletic injuries or headaches.[22,23] For example, one report found that about one half of adolescents who were seen for headaches were given opioids.[24,25] When the origins of misuse are explored, it is clear that some youth begin by using leftovers from their own prescriptions.[26] Unfortunately, early misuse is a risk factor for later heroin use.[27,28]

Percocet was first marketed in 1976. The oxycodone it contains is produced from the opium alkaloid thebaine. Some allege that Percocet's availability from both licit and illicit sources is fueling the current opioid epidemic; it has the reputation of being *white collar* heroin.[29,30] Percocet's availability can be attributed to leftovers from prescriptions, thefts from hospitals and pharmacies, and illegal importation from other countries. Forged prescriptions can also be involved. In the State of Rhode Island, the nationwide pharmacy chain CVS Pharmacy, Inc., recently

paid a fine of more than a half million US dollars for filling forged prescriptions, which it is charged that they should have recognized as such.[31]

CANNABIS/MARIJUANA

A recent unsolicited e-mail I received made an unsupported claim, as shown in the Figure. When I tried to investigate this site, my computer's security programs blocked access to it, and I could not recover its universal resource locator (URL). During the past year, I have received numerous other unsolicited e-mails. A common phrase was frequently used: "…you have been selected to register for CBD [cannabidiol] clinical trials … [this is your] … chance to access available clinical trials near you …. " Almost all of these e-mails came from what appear to be spamming sites (eg, @mx0.occupationonline.com; mx6.adventureseverywhere.com; @mx15.healthylifestyletipz.com; and mx19.suggestsolutions.com). Who selected me and on what basis?

The one e-mail I opened included the following statement: "This HIPAA-compliant, 100% secure site connects people suffering from pain with REAL U.S. Board-Certified Doctors and Licensed Nurses … The results of your Pain Profile may be surprising, so please be cautious when reviewing your profile."[32] This e-mail appeared to come from an organization called LivingWithPain. They described themselves as follows: "We are a health care advocacy organization. We analyze health information and provide customized health solutions for those suffering from pain." Why would anyone give them access to their "Pain Profile" or any other health data? Other obvious questions about this advertisement are: Who are the participating physicians and nurses? Why are they involved with this program? Where are they licensed? Not surprisingly, when I tried to reconnect with the initial website for this Note, I was unable to reestablish a connection. In my efforts to learn more about LivingWithPain, I did find a website containing highly critical comments submitted by individuals who claim that the organization misled them and attempted to sell them CBD.[33]

What are the goals behind such so-called "medical" or "health-related" cannabis advertising? I have never studied marketing or advertising, but some goals are identifiable and make common sense: (1) to educate, inform, or increase awareness—all ways of obtaining the attention of potential patients or users; (2) to motivate, stimulate, and persuade—ways to solicit potential patients to try or use a product; and (3) to remind patients or potential patients or users of availability, and through repeated exposure, to increase brand/product awareness and loyalty. There may be other goals, but for my purposes these will suffice. Are these sites educating or increasing awareness, or are they promoting and soliciting? Are these sites straddling an ethical line?

On April 2, 2019, FDA Commissioner Scott Gottlieb issued a statement mentioning new steps to be taken by the FDA as it continues to evaluate cannabis products.[34] The following step is pertinent to cannabis advertising: The FDA will issue "…multiple warning letters to companies marketing CBD products with egregious and unfounded claims that are aimed at vulnerable populations." He also points out that in the 2018 Farm Bill (the Agriculture Improvement Act of 2018), a new cannabis category was created. Products with <0.3 dry weight concentrations of delta-9-tetrahydrocannabinol (THC) are now to be called "hemp," and, most importantly, hemp is not a federally designated controlled substance.

I continue to be a skeptic about the growing availability and use of increasingly potent cannabis products. Having spoken with a number of city and state regulators, it is my impression that few of them have considered the downside of cannabis use. They seem to me to be motivated at least in part by images of increased taxation revenues and by a widely held belief that cannabis is somewhat comparable to alcohol. I also do not believe that the general

Figure. Excerpt from unsolicted email advertisement for cannabidiol (CBD).

public has adequate knowledge of problems that may result from cannabis use. What follows are some of my remaining questions:

Is marijuana a gateway drug? For the majority of users, the answer appears to be no. However, for a clinically meaningful proportion of users, there is an association between early exposure and subsequent use, misuse, and abuse of other illicit drugs.[35,36] Risk factors for subsequent escalation to other illicit drugs are still unknown. Also, the cannabis landscape is evolving; more potent and more selective products are becoming available.

Will more potent marijuana change the answer?

Do cannabis-vulnerable persons have anything in common with those who have subsequent problems with opioids after early exposure? For these questions and for the following questions, the differential effects from inhaled versus edible products and marijuana per se versus cannabidiol are not established.

Is marijuana use dangerous during pregnancy? As I mentioned in an earlier Note, women are using marijuana during pregnancies, and some dispensaries are even recommending its use for first-trimester nausea.[37] This is worrisome because cannabis use during pregnancy is associated with increased risks for behavioral, cognitive, and brain development concerns in infants; lower birth weights are also reported.[38–44] It is not known how exposure during specific months of pregnancy is related to these outcomes.

Is "vaping" safer than other routes of inhalation? Recently, a friend proudly showed me his elegant e-cigarette (e-cig) device for vaping marijuana. He emphasized that he can regulate both the strength and amount of inhaled product (THC). The regulatory environment for these pen-sized vaporizers is variable across jurisdictions. Some clinician experts particularly worry about the growing use of marijuana e-cigs by teenagers, referring to it as a "youth culture of vaping." Central to this concern is that the tell-tale odor of burned marijuana can be disguised when flavors and deodorants are added, sometimes called stealth vaping.[45,46] Vaporizing devices do not require FDA approval because cannabis products are not FDA-approved drugs with the one exception of cannabidiol (Epidiolex®; Greenwich Biosciences, Inc, Carlsbad, California) for Lennox-Gastaut and Dravet types of epilepsy.[47]

Is marijuana use safe while driving? How does it compare with alcohol use? With regard to the latter question, both impair driving skills as a function of dose and concentration.[48] It is also clear that when both are used, impairment is greater than with either alone. A thoughtful piece of advice is that a person who has been using marijuana should wait at least 2 h before driving and that combined use should be avoided. There appears to be an increase in marijuana-associated automobile accidents in some states (ie, Colorado, Nevada, Oregon, Washington) where medical and recreational cannabis use is legalized.[49,50] The Insurance Institute for Highway Safety and the Highway Loss Data Institute President David Harkey is quoted as saying: "Despite the difficulty of isolating the specific effects of marijuana impairment on crash risk, the evidence is growing that legalizing its use increases crashes." He has also urged states considering the legalization of cannabis use to factor into their deliberations the impact and costs of cannabis use on car crashes.[49] Of added concern is that in ~14% of crashes involving marijuana intoxication, a child was also in the vehicle.[50]

The American Automobile Association recently released a survey in which 3349 respondents were queried about driving and marijuana.[51] This sample consisted of persons ages 16 years and older; it was constructed to be "…a representative sample of households in the United States and recruited using standard probability-based random digit dial (RDD) and address-based sampling method." Although no survey is ever entirely accurate or representative, its findings are worthy of consideration: (1) driving within 1 h after using marijuana was considered to be dangerous by 70% of the sample; (2) a small cohort (7%) believes marijuana use is okay; (3) millennials (born between 1980 and 1994) and Generation Z (born between 1995 and 2015) respondents were the groups most likely to drive immediately after marijuana use, at 14% and 10%, respectively; (4) millennials were the cohort most likely to indicate that they had driven "under the influence of marijuana" at least one or more times in the month preceding the survey (8.5%); and (5) my age cohort (those aged 75 years and older) viewed marijuana use and driving to be quite hazardous.

The Baltimore Sun carried an article about this American Automobile Association report.[52] It was titled "Most Americans Don't Think It's a Problem to Drive High. Here's Why It Is." In the article, the coordinator for Maryland's Drug Recognition Expert Training program is quoted as saying that although driving under the influence of marijuana is as dangerous as alcohol, the impairments are different. He says that trained officers use clues such as

the inability to cross one's eyes, swaying, and difficulty with the finger-to-nose maneuver and that these are different from the balance tests that are used for alcohol. These impairments are consistent with THC's known effects on the cerebellum.[53,54] Their detectability may depend on the strength of the THC concentration consumed. Ramaekers et al[54] have shown this in a study of motor performance in 20 recreational users who smoked cigarettes containing matching placebo, 250 μg/kg THC, or 500 μg/kg THC.

When answering the question of marijuana effects on driving, the Centers for Disease Control and Prevention indicate the following: "…Marijuana use can slow your reaction time and ability to make decisions, impair coordination, distort perception, and lead to memory loss and difficulty in problem-solving. However, although we know marijuana negatively affects a number of skills needed for safe driving, and some studies have shown an association between marijuana use and car crashes, it is unclear whether marijuana use actually increases the risk of car crashes. This is because an accurate roadside test for drug levels in the body doesn't exist."[55]

Another unresolved question is whether and to what degree cannabis use affects sperm health and male fertility rates. There is evidence on both sides of this question.[56–61] It is beyond the scope and space for this Note to thoroughly critique each of these studies.

I will also not be able to discuss the use of cannabis products as a risk factor for the development of psychoses.[62,63] My strong opinion is that we still do not have enough information about who can safely use cannabis products at all or about what amounts or strengths may be the upper tolerability or safety limits for others. In other words, *for whom is cannabis use a medically sound intervention or a completely safe treat versus for whom is it a risky trick?*

Our Update this month was developed by Dr. Jill Maron, our Topic Editor for Youth and Children. She has assembled a group of articles focusing on the detrimental effects of the opioid epidemic on neonates, children, and adolescents.[64–70]

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This month's Youth and Children Update is a special feature which is available as FREE ACCESS content on the journal's website. One of the previous Youth and Children Updates, entitled "Maternal and Childhood Obesity" was published in Volume 40, No. 10 of Clinical Therapeutics. To view the previous Update, see the articles below:

Maron JL. Rethinking Childhood Obesity: Novel Preventive and Treatment Strategies

Agrawal S, Gensure R. Commentary on the Impact of Obesity on Pediatric Diabetes

Barbour LA, Hernandez TL. Maternal Lipids and Fetal Overgrowth: Making Fat from Fat

Chernoguz A, Chwals WJ. Bariatric Surgery Needs a Seat at the Children's Table: Bridging the Perception and Reality of the Role of Bariatric Surgery in the Treatment of Obesity in Adolescents

Ramos-Roman MA. Breast Milk: A Postnatal Link Between Maternal Life Choices and the Prevention of Childhood Obesity

Penfield-Cyr A, Monthe-Dreze C, Smid MC, Sen S. Maternal BMI, Mid-pregnancy Fatty Acid Concentrations, and Perinatal Outcomes